Determining the Trough-to-Peak Ratio in Parallel-Group Trials

Jan A. Staessen, Lutgarde Thijs, Geert Bijttebier, Denis Clement, Eoin T. O'Brien, Paolo Palatini, José L. Rodicio, Joseph Rosenfeld, Robert Fagard, on Behalf of the Systolic Hypertension in Europe (SYST-EUR) Trial Investigators

Abstract We explored how in parallel-group trials interindividual variability, correction for placebo effects, and smoothing of blood pressure profiles can be handled in measuring the trough-to-peak ratio in 244 individuals with isolated systolic hypertension (≥60 years) enrolled in the placebo-controlled Systolic Hypertension in Europe Trial. Net treatment effects were computed by subtracting the mean changes from baseline during placebo (n=133) from those during active treatment (n=111). At entry, systolic/diastolic pressures averaged 176/86 mm Hg in the clinic and 149/80 mm Hg on 24-hour ambulatory monitoring. With corrections applied for baseline and placebo, nitrendipine (10 to 40 mg/d), with the possible addition of enalapril (5 to 20 mg/d) and/or hydrochlorothiazide (12.5 to 25 mg/d), reduced ($P<.001$) these blood pressure values by 16.6/7.3 and 9.8/4.7 mm Hg, respectively. The net trough-to-peak ratios were first determined from blood pressure profiles (12 hours) with 1-hour precision, synchronized by the morning and evening doses of the double-blind medication. According to the usual approach, disregarding interindividual variability, the systolic/diastolic net trough-to-peak ratios were 0.46/0.40 in the morning and 0.77/0.99 in the evening. In individual subjects, the baseline-adjusted trough-to-peak ratios were nonnormally distributed. We therefore used a nonparametric technique to calculate the net trough-to-peak ratios from the results in individual subjects. In the morning, these ratios averaged 0.25 systolic (95% confidence interval, 0.09 to 0.41) and 0.15 diastolic (95% confidence interval, 0.00 to 0.31) and in the evening, 0.19 and 0.36 (95% confidence intervals, 0.00 to 0.38 and 0.14 to 0.56), respectively. When the blood pressure profiles were smoothed by substituting the 1-hour averages by moving or fixed 2-hour averages or by Fourier modeling, the trough-to-peak ratios remained unchanged after the morning dose (0.20/0.13, 0.20/0.14, and 0.16/0.21, respectively) but tended to increase in the evening (0.32/0.38, 0.28/0.40, and 0.48/0.49). In conclusion, the parallel-group analysis proposed makes it possible for one to correct the trough-to-peak ratio for baseline as well as placebo, to account for interindividual variability, and to calculate a confidence interval for the net trough-to-peak ratio. Accounting for interindividual variability reduces the trough-to-peak ratio. Smoothing affects the individualized net trough-to-peak ratios in an unpredictable way and should therefore be avoided. (*Hypertension*. 1997;29:659-667.)

Key Words • blood pressure monitoring, ambulatory • blood pressure • clinical trials

In an attempt to create an operational index of the duration of antihypertensive activity, the Food and Drug Administration introduced the trough-to-peak ratio of blood pressure (BP) responses.[1-4] The American guidelines stipulate that in addition to maintaining a "useful" antihypertensive effect at the end of the dosage interval, the trough effect should be at least half of the peak effect, once appropriate adjustments have been made for placebo. Increasingly, ambulatory BP monitoring is used for determination of the trough-to-peak ratio[5]; however, the original guidelines do not define how interindividual variability, correction for placebo effects, and smoothing of the BP profiles should be dealt with.[1-4] A previous article, in which control and experimental observations were collected in the same subjects,[6] addressed these issues for crossover trials. However, in parallel-group trials, the unit of analysis is the group rather than the individual.

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From the SYST-EUR Trial Investigators; a complete list of the participants in this research study appears at the end of this article.

Correspondence to Jan A. Staessen, MD, PhD, Klinisch Laboratorium Hypertensie, Inwendige Geneeskunde-Cardiologie, UZ Gasthuisberg, Herestraat 49, B-3000 Leuven, Belgium.

The Systolic Hypertension in Europe (SYST-EUR) trial is a double-blind, placebo-controlled outcome trial in older individuals with isolated systolic hypertension that the European Working Party on High Blood Pressure in the Elderly is currently conducting in Western and Eastern Europe and Israel.[7] With more than 4600 individuals randomized, recruitment has been completed. SYST-EUR centers can choose to monitor their subjects in an attempt to evaluate whether the ambulatory BP, over and above the clinic pressure, is helpful in predicting the incidence of cardiovascular events.[8] This article builds on the data collected up to now and explores how in clinical trials with a parallel-group design interindividual variability, correction for placebo effects, and smoothing of BP profiles can be handled in measuring the trough-to-peak ratio.

Methods

Study Design

The protocol of the SYST-EUR trial has been published elsewhere.[7] It was approved by the Ethics Committee of the Faculty of Medicine at the University of Leuven as well as by the institutional review committees of all participating centers. Subjects were eligible (1) if they were at least 60 years old; (2) if on placebo during the run-in phase their sitting systolic pressure ranged from 160 to 219 mm Hg, with diastolic pressure below 95 mm Hg; (3) if their stand-

ing systolic pressure was 140 mm Hg or more; and (4) if they consented to be enrolled. The BP criteria for entry rested on the averages of six sitting and six standing readings, ie, two in each position at three baseline visits 1 month apart.

Eligible subjects were stratified by sex and the presence versus absence of cardiovascular complications and randomized to double-blind treatment with active medication or placebo. Active treatment consisted of nitrendipine (10 to 40 mg/d), if necessary combined with enalapril (5 to 20 mg/d) and/or hydrochlorothiazide (12.5 to 25 mg/d). Control subjects received matching placebos. The study medications were stepwise titrated and combined in an attempt to reduce the sitting systolic pressure by 20 mm Hg or more to a level of less than 150 mm Hg.[7]

Ambulatory BP Measurement

SYST-EUR centers choosing to take part in the ambulatory monitoring project were asked to perform recordings at baseline, at 6 and 12 months, and thereafter annually.[8] Validated[9,10] monitors were programmed to obtain measurements at intervals no longer than 30 minutes. The conventional BP corresponding to each ambulatory recording was the average of the two readings taken with subjects in the sitting position obtained at the nearest clinic visit.

On May 15, 1996, 445 subjects had their ambulatory BP recorded during the run-in phase of the trial and at least once during double-blind treatment. Of the recordings taken during double-blind treatment, only the first was considered for analysis. After subjects with incomplete recordings (n=74) and subjects not on a twice-daily treatment regimen (n=127) were excluded, 244 were left for analysis. The demographic characteristics of the SYST-EUR subjects enrolled in the project on ambulatory BP monitoring have been described in detail elsewhere.[11,12]

Analysis of the Diurnal BP Profile

Database management and statistical analyses were performed with SAS software (SAS Institute Inc). If the ambulatory recordings were longer than 24 hours, only the first 24 hours was analyzed. Recordings were excluded whenever the available readings constituted less than 80% of those programmed or covered less than 22 consecutive hours. The editing criteria[13] that were considered, but actually not applied, removed only 1.5% of the readings without any effect on the findings.[11] Within subjects, the ambulatory measurements were averaged with weights according to the time interval between successive readings.[13] Daytime and nighttime were defined on the basis of short fixed-clocktime intervals,[15,16] which ranged from 10 AM to 8 PM and from midnight to 6 AM, respectively.

Nitrendipine, the first-line calcium entry blocker in the SYST-EUR trial, is characterized by a terminal plasma half-life of 12 hours.[17,18] The trough-to-peak ratios were therefore calculated from BP curves consisting of 12 consecutive hours and synchronized by the hour of intake of the morning and evening medications. Information on dosage was retrieved from the diaries kept by the subjects on recording days. The trough was the blood change during the last period of the dosage interval, ie, the period immediately preceding the next intake of study medication. The term peak refers to the maximal blood fall observed during any other interval considered in a particular analysis. In keeping with the predominant trend in the current literature,[19] the trough and peak effects and their ratios were first determined in all subjects combined (global estimates). In addition, to evaluate the effects of interindividual variability, we also derived these parameters from BP profiles in each subject separately.

Initially, the trough-to-peak ratios were determined from BP profiles with 1-hour resolution. The effects of smoothing were then investigated by substituting the 1-hour means by moving (1-hour steps) or fixed 2-hour averages or by Fourier modeling.[14] Whole-day Fourier curves were fitted in individual subjects by weighted least-squares regression and included four harmonics with periods of 24, 12, 8, and 6 hours, respectively.[14] The peak and trough responses were determined from 12-hour stretches of the whole-day Fourier curves, which had a resolution of 1 minute.

Other Statistical Methods

Because the distributions of the trough-to-peak ratios and the times to peak deviated from normality on the Shapiro-Wilk test,[20] the central tendency and spread of these data were represented by the median and the 5th to 95th percentile interval. In addition, for the trough-to-peak ratios, box plots were constructed.[21] Within each treatment group, the 95% confidence interval (CI) about the median was obtained by calculating the quantities $L=(n/2)-(1.96\times\sqrt{n}/2)$ and $H=(n/2)+(1.96\times\sqrt{n}/2)$ and rounding these values to the nearest integer.[22] The Lth and Hth observation of the ranked trough-to-peak ratios then determined the 95% CI.[22]

Within each treatment group, measurements at baseline were subtracted from the corresponding values at follow-up for all intervals considered in a particular analysis.[1] Net treatment effects were calculated by subtracting the mean change from baseline during placebo from the corresponding change during active treatment.[23] The 95% CIs about the net treatment effects showed when during the dosage interval active treatment produced significant BP changes. For normally distributed variables, such as the hourly BP means and the troughs and peaks, the calculation of the point estimates and 95% CIs of the net treatment effects involved the usual techniques of statistical inference, as described by Armitage and Berry.[24] For nonnormally distributed variables, such as the times to peak and the trough-to-peak ratios, the point estimates and 95% CIs of the net treatment effects were computed according to the method of Campbell and Gardner.[22] Briefly, suppose that "a" and "p" are the numbers of subjects in the active treatment and placebo groups, respectively, that $A_1, A_2, \ldots, A_a$ are the trough-to-peak ratios in "a" actively treated subjects, and that $P_1, P_2, \ldots, P_p$ are the corresponding ratios in "p" subjects on placebo. Then in an array with $a\times p$ elements, all possible differences $(A_1, A_2, \ldots, A_a - P_1, P_2, \ldots, P_p)$ were calculated. The median of these differences provided the point estimate of the net trough-to-peak ratio. The 95% CI was given by the ranks K and $(a\times p)-K+1$, where $K=[(a\times p)/2]-(1.96\times[a\times p\times(a+p+1)/12]^{1/2}$, rounded to the next integer.

For pairwise comparisons, Wilcoxon's signed rank test was used if the variables were nonnormally distributed and Student's t test otherwise. Proportions were compared using the standardized normal deviate. BP profiles with 1-hour precision were contrasted by repeated measures ANOVA,[25] considering as main effects treatment allocation (active versus placebo) and time after intake of the study medication. To establish whether the antihypertensive action was steady throughout the dosage interval, we also tested the model for a treatment-time interaction.

Results

Subject Characteristics at Randomization

The subjects allocated to placebo (n=133) or active treatment (n=111) had the same characteristics at randomization (Table 1). They comprised 107 men and 137 women. Cardiovascular complications were present in 71 subjects. Of the 244 subjects, 128 had been treated for hypertension within 6 months before they were considered for enrollment into the run-in phase of the trial. Age averaged (±SD) 70±6 years (range, 60 to 100). Body mass index was 26.2±3.4 kg/m^2 in men and 26.8±4.1 in women. BP at the clinic averaged 176±13 mm Hg (range, 160 to 217) systolic and 86±6 (49 to 94) diastolic. The 24-hour BPs were 149±15 mm Hg (117 to 202) and 80±9 (58 to 107), respectively (Table 1).

Effects of Treatment on BP

Follow-up of double-blind treatment lasted a median of 7 months (range, 2 to 34). The 111 actively treated subjects

TABLE 1. Conventional and Ambulatory Blood Pressures at Baseline and Follow-up

Characteristic	Baseline		Follow-up		Net Difference (Active−Placebo)
	Placebo	Active	Placebo	Active	
n	133	111	133	111	244
Baseline characteristics					
Men, %	45.8	41.4	...	...	−4.4 (−16.9, 8.1)
CV complications, %*	27.1	31.5	...	...	4.4 (−7.0, 15.9)
Age, y	70±7	70±6	...	...	−0.3 (−1.9, 1.3)
Body mass index, kg/m²	26.8±3.8	26.3±3.8	...	...	−0.5 (−1.5, 0.5)
Systolic pressure, mm Hg					
Clinic	175±11	178±14	167±20	154±17	−16.6 (−20.7, −12.5)
24-Hour	148±14	150±15	147±15	139±13	−9.8 (−13.0, −6.5)
Daytime	154±15	155±17	153±17	145±14	−9.3 (−13.3, −5.4)
Nighttime	135±17	138±19	134±18	128±17	−8.2 (−12.0, −4.3)
12 Hours after medication					
Morning dose	155±19	157±22	154±21	148±18	−7.7 (−13.3, −2.1)
Evening dose	146±23	147±23	146±21	137±18	−9.9 (−15.3, −4.5)
Diastolic pressure, mm Hg					
Clinic	87±6	85±6	86±8	77±10	−7.3 (−9.5, −5.1)
24-Hour	80±9	79±8	80±9	74±8	−4.7 (−6.5, −3.0)
Daytime	85±10	84±10	84±10	79±9	−4.9 (−7.0, −2.7)
Nighttime	71±10	70±11	70±10	66±10	−3.1 (−5.3, −1.0)
12 Hours after medication					
Morning dose	84±13	84±13	84±13	80±11	−4.3 (−8.0, −0.5)
Evening dose	79±14	79±17	81±14	74±15	−6.4 (−10.7, −2.2)

CV indicates cardiovascular. Daytime was defined as 10 AM to 8 PM and nighttime as midnight to 6 AM. Values are percentages, mean±SD, or mean differences with 95% confidence interval in parentheses. All net blood pressure differences were significant at 0.1%.

*Cardiovascular complications at entry included Sokolow-Lyon index ≥35 mm, coronary heart disease, angina pectoris, or history of myocardial infarction or minor stroke more than 1 year before enrollment in the run-in phase.

took their medications at 8:30 AM (median) (range, 7 AM to 2 PM) and 9 PM (3:30 PM to 2 AM). Nitrendipine in the morning and evening was combined with enalapril administered in the morning in 2 subjects, in the evening in 25, and twice daily in 10. Twelve subjects also received hydrochlorothiazide in the morning. The daily doses of the first-, second-, and third-line study medications averaged 32±10, 14±7, and 20±6 mg, respectively. The 133 placebo-treated subjects took their medications at 9 AM (7 AM to 2 PM) and 9 PM (3:30 PM to 12:15 AM). The nitrendipine placebo tablets were combined with placebos matching enalapril and hydrochlorothiazide in 71 and 26 subjects, respectively.

After correction for baseline and placebo, the net BP reductions during active treatment ($P<.001$) averaged 16.6 mm Hg systolic and 7.3 diastolic for the clinic pressures and 9.8 and 4.7 for the 24-hour pressures (Table 1). The baseline and follow-up BP curves were synchronized by the hours of intake of the study medications in the morning and evening. The calculations of the morning trough-to-peak ratios will be illustrated in detail, whereas those of the evening ratios will be summarized.

Trough-to-Peak Ratio After Morning Dose of Study Medication

BP Profiles at Baseline and Follow-up

At both baseline and follow-up, the time elapsed from the morning dose was a significant source ($P<.001$) of BP variation. At baseline, treatment allocation (systolic pressure, $P=.54$; diastolic pressure, $P=.97$) as well as the treatment-time interaction terms ($P=.90$ and .81, respectively) were not significant. Thus, during the run-in phase, the synchronized BP profiles were superimposable in the two treatment arms (Fig 1).

At follow-up, active treatment shifted ($P<.001$) the systolic and diastolic BP profiles downward (Fig 1). The significant treatment-time interactions ($P=.003$ and .002) confirmed the visual impression that on average, the BP differences between the two treatment groups went through a maximum of 2 to 4 hours after intake of the morning medication (Fig 1).

Morning Trough-to-Peak Ratios in the Global Approach

To correct for baseline, we subtracted the 1-hour BP means during placebo run-in medication from the corresponding values at follow-up (Fig 2, left). From these curves, the trough-to-peak ratios were determined in the two treatment groups separately. In the subjects on double-blind placebo, the morning ratios were 0.17 systolic (Table 2) and 0.12 diastolic (Table 3). In the actively treated subjects, these values were 0.43 and 0.46, respectively.

In the next step of the analysis, the 1-hour net treatment effects were obtained by subtracting the systolic and diastolic pressure changes in the placebo group from those observed in the active treatment group (Fig 2, right). Visual analysis of the resultant curve enabled global determination of net troughs and peaks. Their ratios were 0.46 systolic (Table 2) and 0.40 diastolic (Table 3).

Morning Trough-to-Peak Ratios in the Individual Approach

The first step in the individual approach was the subtraction in each subject of the BP curve at baseline from the corresponding profile during randomized treatment (Fig 3). This made possible calculation of the trough-to-peak ratios in individual subjects allocated to either placebo or active treatment. In the two treatment arms of the

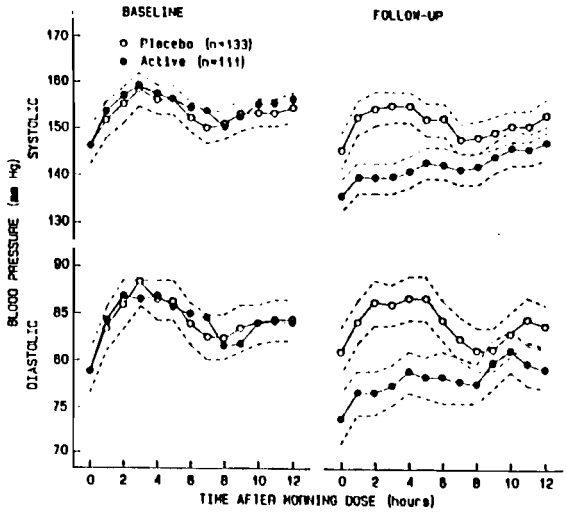

FIG 1. Systolic (top) and diastolic (bottom) blood pressure profiles up to 12 hours after the morning dose of the study medication at baseline (left) and follow-up (right) in 244 older individuals with systolic hypertension. Hourly blood pressure means are expressed with 95% confidence intervals.

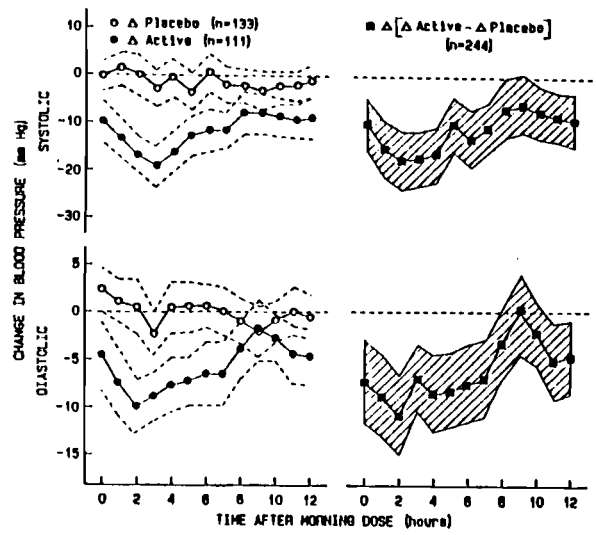

FIG 2. Changes from baseline to follow-up in hourly blood pressure means up to 12 hours after the morning dose of the study medication (left) in subjects allocated to placebo or active treatment. Net treatment effects were obtained (right) by subtracting mean changes from baseline during placebo from corresponding changes during active treatment. Statistics are means with 95% confidence intervals. In the global approach, troughs and peaks were determined from the graphs in the right panel of the figure (see Tables 2 and 3).

trial, the distributions of the individual trough-to-peak ratios deviated ($P<.001$) from normality (Fig 4, top). In some subjects, BP at the end of the dosage interval was higher at follow-up than at baseline, explaining why their baseline-adjusted ratios were negative (positive denominator divided by negative nominator).

The global and individual approaches resulted in similar estimates of the troughs (Tables 2 and 3) because they were always determined at the last interval preceding the next dosage. In contrast, because of the large intraindividual variability in the magnitude and timing of the peaks, the individualized compared with the global calculations yielded widely different estimates of the times to peak and the peaks and hence the trough-to-peak ratios (Tables 2 and 3).

TABLE 2. Effects of Morning Dose of Study Medication on Systolic Pressure Profiles With 1-Hour Resolution

	Global Estimates*		Individual Estimates†	
Blood Pressure	**PE**	**95% CI**	**PE**	**95% CI**
Placebo (n=133)				
Peak, mm Hg	−3.3	−7.2, 0.6	−29.9±18.2	−33.0, −26.8
Time to peak, h:min	4:30	NA	5:30 0:30, 10:30	4:30, 6:30
Trough, mm Hg	−0.5	−4.0, 2.9	−0.5±20.5	−4.0, 2.9
Trough-to-peak ratio	0.17	NA	−0.03 −1.64, 1.00	−0.16, 0.08
Active treatment (n=111)				
Peak, mm Hg	−19.0	−23.2, −14.8	−40.7±19.6	−44.3, −37.0
Time to peak, h:min	2:30	NA	3:30 0:30, 11:30	2:30, 4:30
Trough, mm Hg	−8.3	−12.7, −3.9	−8.3±23.6	−12.7, −3.9
Trough-to-peak ratio	0.43	NA	0.22 −0.68, 1.00	0.13, 0.33
Net effects (n=244)				
Peak, mm Hg	−16.9	−23.0, −10.8	−10.8±2.4‡	−15.6, −6.0
Time to peak, h:min	1:30	NA	−1:00§	−2:00, 0:00
Trough, mm Hg	−7.7	−13.3, −2.1	−7.8±2.9‡	−13.3, −2.1
Trough-to-peak ratio	0.46	NA	0.25§	0.09, 0.41

PE indicates point estimate; CI, confidence interval; and NA, not available.

*PE and CI derived from treatment effect curve in all subjects combined (see Fig 2, right).

†PE and CI derived from data in single subjects. The statistics are arithmetic mean±SD for peaks and troughs and medians with 5th to 95th percentile intervals for times to peak and trough-to-peak ratios.

‡Differences in group mean±SE as described by Armitage and Berry.[24]

§Differences in medians according to Campbell and Gardner.[22]

According to the nonparametric technique used in the present article, the medians of all possible differences between the subjects on placebo and active treatment reflected the baseline- and placebo-corrected net treatment effects (Fig 4, bottom). For the morning trough-to-peak ratios, these parameters were 0.25 for systolic (Table 2) and 0.15 for diastolic (Table 3) BP. The CIs indicated that the two ratios were significantly larger during active than placebo treatment.

Smoothing of the Morning BP Profiles in the Individual Approach

We increasingly smoothed the treatment effect curves by substituting the 1-hour BP averages by moving or fixed 2-hour averages or by Fourier modeling. Within each treatment group, smoothing did not affect the estimates of the trough effect (Fig 5). In contrast, in both the placebo and active treatment groups, the apparent peak effects became smaller ($P<.001$) with smoothing. However, smoothing did not materially alter the resultant within-group ratios (Fig 5) and the overall net ratios (Table 4).

Trough-to-Peak Ratio After Evening Dose of Study Medication

The trough-to-peak ratios were also computed from 12-hour BP profiles with 1-hour resolution recorded after the evening dose of the study medication. As for the net morning ratios, the baseline- and placebo-adjusted evening ratios were substantially larger in the global than in the individualized approach. The net ratios were 0.77 systolic and 0.99 diastolic and 0.19 (95% CI, 0.00 to 0.38) and 0.36 (95% CI, 0.14 to 0.56), respectively.

The baseline- and placebo-adjusted trough-to-peak ratios increased systolic to 0.32 (95% CI, 0.10 to 0.54), 0.28 (95% CI, 0.00 to 0.52), and 0.48 (95% CI, 0.25 to 0.70) and diastolic to 0.38 (95% CI, 0.14 to 0.57), 0.40 (95% CI, 0.16 to 0.61), and 0.49 (95% CI, 0.27 to 0.71), respectively, for smoothed profiles consisting of moving or fixed 2-hour averages or of values derived by Fourier modeling.

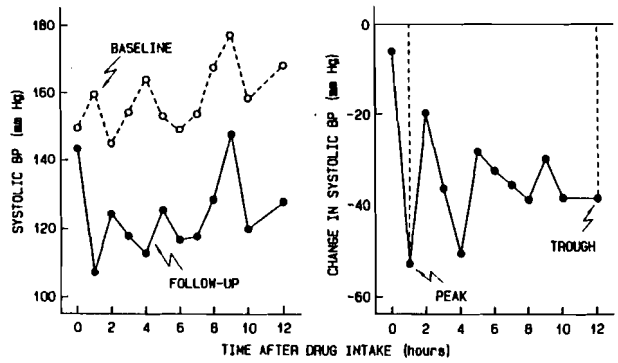

FIG 3. Baseline and follow-up recordings of systolic blood pressure (BP) in a single subject. Subtracting the baseline from the follow-up data resulted in the individual treatment effect curve (right) from which the peak, trough, and trough-to-peak ratios were determined. The median of all individual trough-to-peak ratios was subsequently calculated (see Fig 4).

Discussion

We analyzed the SYST-EUR[7,8] database to test how in randomized clinical trials with a parallel-group design interindividual variability, correction for baseline and placebo, and smoothing of the BP profiles can be handled in the determination of trough-to-peak ratio. The SYST-EUR trial, an outcome trial in isolated systolic hypertension, was not designed to evaluate the duration of action of antihypertensive agents. Although the treatment regimens were based on nitrendipine or matching placebo, some subjects also received second- and/or third-line medications in the morning or evening. The BP curves were synchronized by the hour of intake of the study medication. However, these times ranged from 7 AM to 2 PM for the morning profiles and from 3:30 PM to 2 AM for the BP curves registered in the evening. These particular characteristics of the SYST-EUR trial may explain the somewhat diverging results for the morning and evening profiles. Insufficient standardization may also have inflated the intra-

TABLE 3. Effects of Morning Dose of Study Medication on Diastolic Pressure Profiles With 1-Hour Resolution

	Global Estimates*		Individual Estimates†	
Blood Pressure	**PE**	**95% CI**	**PE**	**95% CI‡**
Placebo (n=133)				
Peak, mm Hg	−2.3	−4.6, 0.1	−21.1±13.4	−23.4, −18.8
Time to peak, h:min	2:30	NA	6:30 0:30, 11:30	4:30, 7:30
Trough, mm Hg	−0.3	−2.6, 2.1	−0.3±13.7	−2.6, 2.1
Trough-to-peak ratio	0.12	NA	0.01 −1.93, 1.00	−0.09, 0.17
Active treatment (n=133)				
Peak, mm Hg	−9.9	−12.8, −7.1	−29.3±18.0	−32.7, −26.0
Time to peak, h:min	1:30	NA	5:30 0:30, 11:30	3:30, 5:30
Trough, mm Hg	−4.5	−7.4, −1.6	−4.5±15.7	−7.4, −1.6
Trough-to-peak ratio	0.46	NA	0.12 −1.07, 1.00	−0.03, 0.23
Net effects (n=304)				
Peak, mm Hg	−10.6	−14.7, −6.4	−8.2±2.1‡	−12.3, −4.2
Time to peak, h:min	1:30	NA	−1:00§	−1:00, 0:00
Trough, mm Hg	−4.3	−8.0, −0.5	−4.3±1.9‡	−8.0, −0.5
Trough-to-peak ratio	0.40	NA	0.15§	0.00, 0.31

Abbreviations and footnotes as in Table 2.

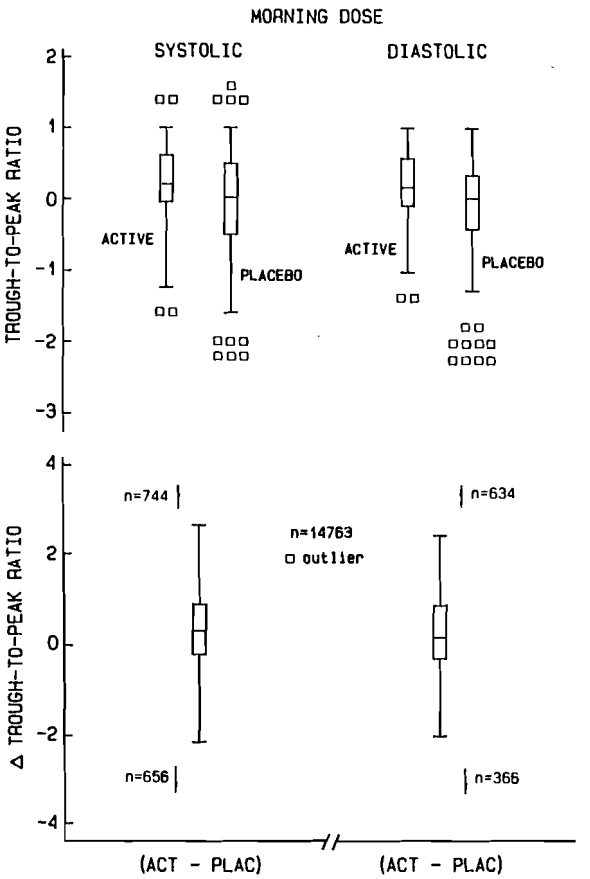

FIG 4. Box plots (top) reporting medians, 25th to 75th percentiles, inner fences (quartiles plus 1.5 times the interquartile range),[21] and outlying values for trough-to-peak ratios in subjects allocated to placebo (PLAC) (n=133) or active treatment (ACT) (n=111). Systolic (left) and diastolic (right) ratios, corrected for baseline, were derived in individual subjects from blood pressure profiles with 1-hour resolution recorded up to 12 hours after the morning dose of the study medication. Net effects of treatment (bottom) were obtained by subtracting the observations during placebo from those during active treatment according to the method of Campbell and Gardner.[22]

individual and interindividual variabilities in the trough-to-peak ratio.

From a pharmacodynamic point of view, the interpretation of the present findings is limited. The results cannot be generalized to describe the pharmacological properties of nitrendipine or the other antihypertensive agents used. Nevertheless, the statistical approach presented in this article is applicable to any pharmacological study with a parallel-group design, which would focus specifically on the duration of action of an antihypertensive agent. The first step in a parallel-group analysis involves computation of the summary statistics for the experimental groups. For variables with a normal distribution, such as BP change from baseline to follow-up, these parameters include the mean and SD. For nonnormally distributed variables, such as the time to peak or trough-to-peak ratio, the median with its 5th to 95th percentile interval constitutes a reasonable alternative.

From a mechanistic point of view, the statistical analyses follow a similar path in crossover studies[6] and within the groups of a parallel-group trial. However, the former design is a special case of a randomized controlled study,[26] whereas within the arms of a parallel-group experiment, baseline invariably precedes intervention. Formal randomization is required for construction of unbiased statistical tests and drawing of valid conclusions. As shown by a review on calcium entry blockers,[19] several parallel-group trials reported only within-group contrasts between baseline and follow-up and did not produce the between-group comparisons to be expected on the basis of randomization. Such analyses cannot produce valid conclusions.[26,27] As the present study illustrates, the technique proposed by Campbell and Gardner[22] makes possible the development of the between-group analysis of nonnormally distributed variables in a way analogous to the usual approach for BP changes, thereby fully respecting the principles of randomization.

The trough-to-peak ratio is a signed variable, because the BP at follow-up is subtracted from the corresponding baseline BP. This difference is likely to be negative in most individuals allocated to active treatment, especially at peak when the BP response is maximal. However, the BP at baseline may also be lower than at follow-up. This situation may occur in the placebo group as well as in the actively treated group, for instance at trough when the dosage interval has been stretched beyond reasonable limits

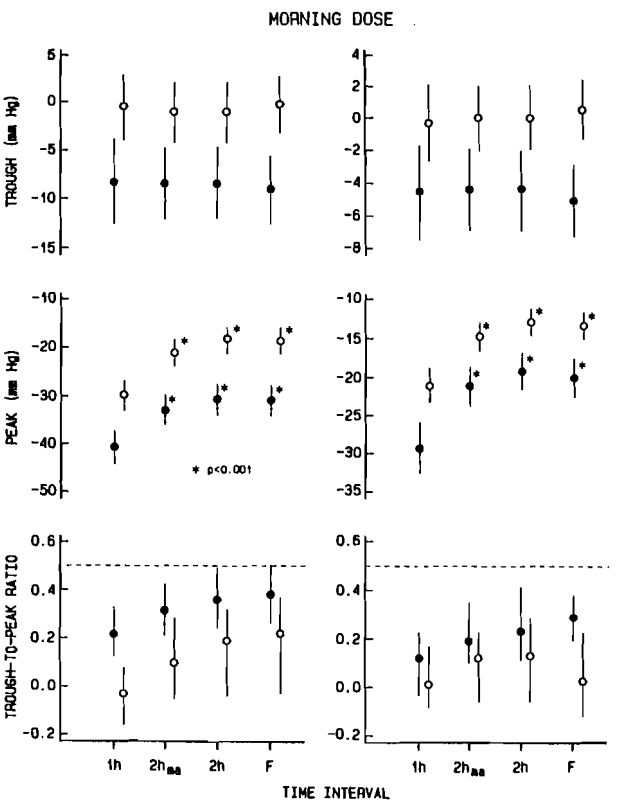

FIG 5. Mean trough and peak reductions in systolic (left) and diastolic (right) pressures and corresponding median trough-to-peak ratios during placebo (n=133, ○) or active treatment (n=111, ●). The statistics, presented with 95% confidence intervals, were derived from 12-hour blood pressure profiles recorded in individual subjects after intake of the morning dose of the study medication. Smoothed profiles consisted of fixed (2h) or moving ($2h_{ma}$) 2-hour blood pressure averages or were derived by Fourier modeling (F).[14] *$P<.001$ vs profiles with 1-hour resolution (1h).

TABLE 4. Net Effects of Morning Dose of Study Medication as Determined in the Individual Approach From Smoothed Blood Pressure Profiles

	2-Hour Moving Averages*		2-Hour Averages		Fourier Modeling	
Blood Pressure	**PE†**	**95% CI**	**PE**	**95% CI**	**PE**	**95% CI**
Systolic pressure						
Peak, mm Hg	−11.7±2.1	−15.8, −7.5	−12.0±2.1	−16.2, −7.9	−12.1±2.1	−16.3, −7.8
Time to peak, h:min	−1:00	−2:00, 0:00	−2:00	−2:00, 0:00	−0:58	−1:55, 0:00
Trough, mm Hg	−7.4±2.5	−12.3, −2.5	−7.4±2.5	−12.3, −2.5	−8.8±2.4	−13.4, −4.1
Trough-to-peak ratio‡	0.20	0.03, 0.38	0.20	0.01, 0.40	0.16	0.00, 0.35
Diastolic pressure						
Peak, mm Hg	−6.4±1.6	−9.5, −3.3	−6.4±1.5	−9.3, −3.4	−6.7±1.5	−9.8, −3.7
Time to peak, h:min	−1:00	−2:00, 0:00	−2:00	−2:00, 0:00	−1:00	−2:05, 0:00
Trough, mm Hg	−4.5±1.6	−7.6, −1.3	−4.5±1.6	−7.6, −1.3	−5.6±1.5	−8.5, −2.8
Trough-to-peak ratio	0.13	−0.02, 0.30	0.14	0.03, 0.34	0.21	0.03, 0.40

Abbreviations as in Table 2.
*2-hour averages moving 1 hour at a time.
†PE and 95% CI rest on data obtained in individual subjects. Values are mean between-group differences±SE[24] for troughs and peaks and median between-group differences[22] for times to peak and trough-to-peak ratios.

or in uncompliant subjects after a drug holiday. In all these cases, the denominator of the trough-to-peak ratio becomes positive, the nominator becomes negative, and hence, the ratio itself is negative.[6,28,29]

In many articles,[30-36] the trough-to-peak ratio was calculated by the global approach, ie, by dividing the average trough by the average peak. Some investigators found this method appropriate in analyses restricted to responders.[29] However, BP is characterized by high intraindividual and interindividual variabilities, of which the diurnal rhythm is an important component. There are also large circadian[37] and between-subject variations in the pharmacokinetics of drugs and in the pathophysiological mechanisms that sustain the elevated BP through the day. Against this background, trough-to-peak ratios must account for intraindividual and interindividual variabilities. Global estimates force all subjects onto the same time scale and flatten the overall peak because the common time to peak and the individual times to peak are not the same. Thus, by definition, peaks must be smaller and trough-to-peak ratios larger in the global than in the individual approach. The former thereby makes it easier for one to reach the arbitrary thresholds recommended by the Food and Drug Administration.[1-4]

In general, trough-to-peak ratios also increase as the intervals making up the BP profiles are extended. Indeed, smoothing reduces the apparent peaks, because each person's maximal BP response is averaged over a longer time period, which is more likely to encompass submaximal BP responses. This concept[6,38] was corroborated in the within-group analyses of the present study (Fig 5). However, in the between-group analyses, smoothing did not affect the trough-to-peak ratios in a consistent manner. Some experts[29] have suggested that troughs and peaks should be computed over 2-hour windows in order to strike the best balance between a correct estimate of the peaks and reproducibility. However, the calculations in the latter study[29] forced peaks to occur within 1, 2, 4, or 6 hours after dosage. No information was provided on how often the peaks actually fell outside these windows or occurred later than 6 hours after dosage.[29] In pharmacological studies with supervised drug intake, forcing the peak to occur within a certain time window after dosage has the advantage of excluding artifacts that are not compatible with the metabolic profile and plasma half-life of the antihypertensive agent under study. For clinical studies in which drug intake cannot be supervised or fully standardized, such as the SYST-EUR trial, defining the peak as the maximal BP fall during any interval other than the trough may be better, because under these conditions the use of a time window may introduce bias. However, the latter approach may also emphasize the peaks and decrease the apparent trough-to-peak ratios by including in the calculations not only the drug-induced maximal BP changes but also a number of randomly or behaviorally induced peaks.

In some articles, subjects were subdivided into responders and nonresponders[39,40] or only responders were included.[41] The exclusion of nonresponders may be attractive from a pharmacodynamic point of view[29]; however, randomized clinical trials have a prospective dimension, and the primary and subsidiary research questions must be stated in advance.[26] Accordingly, if nonresponders are to be excluded, this requirement should be part of the research question and addressed by the screening procedures before enrollment of eligible subjects. Furthermore, clinicians have to deal with unselected subjects. They are not helped by knowing the trough-to-peak ratio in responders only, because in their day-to-day practice, they cannot select such individuals in advance. Moreover, the scale of BP responses is continuous rather than dichotomous.

The present observations reinforce previously made recommendations.[6,28,42] The trough-to-peak ratio, adjusted for placebo effects,[1-3,43] should be calculated from BP profiles in individual subjects, and its distribution must be presented. This approach explores the full range of values of the trough-to-peak ratio. Intraindividual and interindividual variabilities in the ratio are a major problem facing decision makers, with the technique of ambulatory BP monitoring highlighting rather than resolving this problem. The procedures used for the determination of the trough-to-peak ratio must be thoroughly regulated so that diverse studies and agents can be easily compared and experiments and analyses cannot be adapted to suit the needs of a particular antihypertensive agent. If properly determined and reported with a CI, the trough-to-peak ratio is a useful clinical index. Together with the absolute trough and peak, it informs clinicians on the range of re-

sponses to be expected in the majority of hypertensive individuals. From this point of view, there is no need to define a critical threshold. However, measurement of the trough-to-peak ratio with its CI would require large-scale application of ambulatory BP monitoring in randomized clinical trials with a sufficient sample size.[38]

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Participating Centers

On May 15, 1996, the following individuals and centers with randomized subjects participated in the project on 24-hour ambulatory BP monitoring: in Belgium: Leszek Bieniaszewski, Geert Bijttebier (usual affiliation: ZENECA, Destelbergen, Belgium), Hilde Celis, Robert Fagard, Jan A. Staessen, Roger Van Hoof (Leuven), Paul De Cort (Kumtich), Dirk Staessen, and Jan A. Staessen (Mechelen); in Bulgaria: Boyan Shahov (Sofia); in Estonia: Tovio Laks (Tallinn); in Finland: Kari Halonen (Kunsankoski), Tapio Hakamäki, Aapo Lehtonen (Turku), Matti Jääskivi, Liisa Tiito-Wiht, Cinzia Sarti (Vantaa), Pavla Kivinen (Kuopio), Erkki Lehtomäki (Tampere), Reijo Tilvis, Hannu Vanhanen (Helsinki), and Hannu Wallinhiemo (Helsinki); in Germany: Eberhard Ritz (Heidelberg); in Greece: Aris D. Efstratopoulos (Athens); in Ireland: Neil Atkins and Eoin T. O'Brien (Dublin); in Israel: Joseph Rosenfeld, José Zabludowski (Petha Tiqva), and Serge Zerapha (Givataim); in Italy: Alfredo Bossini (Rome), Roberto Fogari (Pavia), Salvatore Lattuada (Milan), Giuseppe Maiorano (Bari), Paolo Palatini (Padova), Anna Pirrelli (Bari), Antonio Salvetti (Pisa), Laura Terzoli (Milan), and Alvaro Vaccarella (Casatenovo); in the Netherlands: Peter de Leeuw (Maastricht), Anton H. van den Meiracker (Rotterdam), and Arend J.J. Woittiez (Almelo); in Poland: Kalina Kawecka-Jaszcz (Cracow) and Jozef Kocemba (Cracow); in Portugal: Gago Leira (Faro); in Slovenia: Jurij Dobovisek (Ljubljana); in Spain: Blas Gil-Extremera (Granada), Rafael Marin (Oviedo), Joan Ocón-Pujadas (Barcelona), Josep Redón (Sagunto), and José L. Rodicio (Madrid); and in the United Kingdom: Garreth Beevers, Monique Beevers (Birmingham), Christopher J. Bulpitt (London), Christopher Davidson (Brighton), Pandita Gunawardena (London), and John Webster (Aberdeen).

Committees and Coordination

Data Monitoring Committee: Christopher J. Bulpitt, Astrid E. Fletcher, Jan A. Staessen, and Lutgarde Thijs; Endpoint Committee: Peter de Leeuw, Robert Fagard, Gastone Leonetti, and James C. Petrie; Ethics Committee: Willem H. Birkenhäger, Collin T. Dollery, and Robert Fagard; European Union SYST-EUR Liaison Committee: Willem H. Birkenhäger, Fernando De Padua, Collin T. Dollery, Aris D. Efstratopoulos, Robert Fagard, Françoise Forette, Detlev Ganten, Eoin T. O'Brien, Kevin O'Malley, José L. Rodicio, Jaakko Tuomilehto, Charles van Ypersele, and Alberto Zanchetti; Publication Committee: Willem H. Birkenhäger, Christopher J. Bulpitt, Jan A. Staessen, and Alberto Zanchetti; Steering Committee: Paul De Cort, Robert Fagard, Françoise Forette, Kalina Kawecka-Jaszcz, Gastone Leonetti, Choudomir Nachev, Eoin T. O'Brien, José L. Rodico, Joseph Rosenfeld, Jaakko Tuomilehto, John Webster, and Yair Yodfat; Trial Coordinators: Robert Fagard and Jan A. Staessen; Coordinators of the Project on Ambulatory Blood Pressure Monitoring: Denis Clement, Eoin T. O'Brien, Giuseppe Mancia, Gianfranco Parati, Jan A. Staessen, and Lutgarde Thijs; Coordinator of the Project on Vascular Dementia: Françoise Forette; Coordinators of the Project on Quality of Life: Christopher J. Bulpitt and Astrid E. Fletcher; and Coordinator of General Practices: Hilde Celis.

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